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(19)

(54) MANUFACTURE OF PYRAZINES

(71) We, BASF AKTIENGESELLSCHAFT, a German Joint Stock Company of 6700 Ludwigshafen, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following Statement:—

The present invention relates to a process for the manufacture of pyrazines.

It is known that 2,5-disubstituted and 2,3,5,6-tetrasubstituted pyrazines may be manufactured by condensing two molecules of an α-aminoketone. The dihydropyrazines first formed can be dehydrogenated by oxidizing agents, e.g. hydrogen peroxide or mercury salts. In another process, α-hydroxyketones are heated with ammonium acetate (Bull. Soc. Chim. France (1965), 3476—3478).

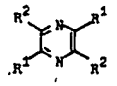
The syntheses of substituted pyrazines suffer from the disadvantage that α-hydroxyketones and, above all, α-aminoketones cannot be manufactured simply and in good yield, especially on an industrial scale.

Houben-Weyl, Methoden der Organischen Chemie, Volume 11/1, page 311 discloses that ammonia reacts with ethylene oxide, even if the former is present in excess, to give a mixture of β-aminoethyl alcohol, diethanolamine and triethanolamine. It is pointed out that it is impossible to control the reaction so as to produce one of the bases only. At the same time, some of the ethylene oxide can react further to form hydroxyethyl ethers.

The present invention seeks to provide a new process for the manufacture of pyrazines.

We have found that pyrazines may be obtained in an advantageous manner by the reaction of 2-nitro-oxiranes bearing a free hydrogen atom in the 3-position with ammonia.

By the process of the invention it is possible to obtain pyrazines of the formula



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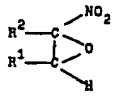
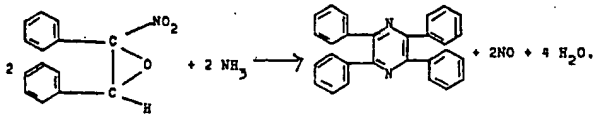
where the R^1's and R^2's are identical or different and each is hydrogen or an aliphatic, cycloaliphatic, araliphatic or aromatic radical and furthermore each R^1 and the adjacent R^2 together with the two carbon atoms joining the two radicals may be members of an alicyclic ring, from 2-nitrooxiranes of the formula



where R^1 and R^2 have the above meanings.

Where 2-nitro-2,3-diphenyl-oxirane is used, the reaction may be represented by the following equation:



In comparison to the conventional processes, the process of the invention surprisingly can be used to produce a large number of pyrazines more simply and more economically, and in better yield and higher purity, even on an industrial scale. The starting materials are readily obtainable and may be manufactured simply and in high yield, e.g. from corresponding nitroolefins by reaction with aqueous hydrogen peroxide, of from 10 to 30 percent strength by weight, and dilute sodium hydroxide solution in polar solvents such as water, methanol, dioxane and diethyl ether, e.g. in accordance with the process described in Zh. Org. Khim., *8* (1972), 2325—2327 (English Edition, pages 2371 to 2373). A further advantage is that the reaction mixture obtained by reaction of the nitrooxiranes with ammonia is simple to work up. No significant formation of a mixture of heterogeneous by-products such as monoalkanol, dialkanol and trialkanol derivatives of ammonia and hydroxyethyl ethers is observable. In the light of the state of the art, all these advantageous results shown by the process are surprising.

The 2-nitrooxirane starting material may be reacted with ammonia in the stoichiometric amount or with an excess of either ingredient. Preferably, however, from 5 to 50 moles of ammonia are used per mole of 2-nitrooxirane. Preferred 2-nitrooxirane starting materials and, accordingly, preferred pyrazine end products are those of the formulae II and I, respectively, where the R^1's and R^2's are identical or different and each is alkyl of 1 to 10, preferably of 1 to 4, carbon atoms, cyclopentyl, cyclohexyl, aralkyl of 7 to 12 carbon atoms, phenyl, naphthyl or hydrogen and furthermore each R^1 and the adjacent R^2 together with the two adjacent carbon atoms may form an alicyclic ring of from 5 to 12, especially of 5 or 6, members. The above radicals and rings can in addition be substituted by groups and/or atoms which are inert under the reaction conditions, e.g. alkyl or alkoxy of 1 to 4 carbon atoms, or nitro.

Examples of 2 - nitrooxirane starting materials are: 2 - nitro - 2 - methyl - oxirane, 2 - nitro - 2 - phenyl - oxirane, 3 - nitro - 3 - methyl - 2 - cyclohexyl - oxirane, 3 - nitro - 3 - methyl - 2 - phenyl - oxirane, 3 - nitro - 3 - ethyl - 2 - phenyl - oxirane, 3 - nitro - 3 - ethyl - 2 - [*p* - methoxyphenyl] - oxirane, 2 - nitro - 2,3 - diphenyl - oxirane, 2 - nitro - 2,3 - dimethyl - oxirane, 2 - nitro - 2,3 - tetramethyleno - oxirane, 2 - nitro - 2,3 - hexamethyleno - oxirane, 2 - nitro - 2,3 - decamethyleno - oxirane, 2 - nitro - 2,3 - trimethyleno - oxirane, 3 - nitro - 2 - benzyl - oxirane, 3 - nitro - 2 - *p* - nitro - phenyl - oxirane, 3 - nitro - 2 - cyclopentyl - oxirane, 2 - nitro - 2 - decyl - oxirane, 2 - nitro - 2 - n - propyl - oxirane and 2 - nitro - 2 - n - butyl - oxirane.

Regarding the manufacture of cycloaliphatic 2 - nitrooxiranes of the formula II in which R^1 and R^2 and the linking carbon atoms form an alicyclic ring, reference may be made to German Laid-Open Patent Application No. 2,425,356, which discloses their, manufacture from the corresponding 1-nitrocycloalkenes by reaction with hydrogen peroxide in the presence of inorganic basic compounds. The nitroolefins 1,2-disubstituted by aromatic and/or aliphatic radicals, which are required for the manufacture of the 2-nitrooxiranes, may be obtained by reaction of unsubstituted or substituted aromatic aldehydes with nitroalkanes, nitroolefins with aliphatic substituents may be manufactured by dehydration of the corresponding nitro alcohols and cycloaliphatic nitroolefins may be manufactured by reaction of cycloalkenes with dinitrogen tetroxide in the presence of bases.

The reaction is in general carried out at from 20 to 200°C, preferably from 40 to 100°C, under atmospheric or superatmospheric pressure, preferably at from 10 to 100 atmospheres, and continuously or batchwise. If necessary, solvents which are inert under the reaction conditions are used to dissolve or suspend the starting mixture and reaction mixture. It is advantageous to use organic solvents which are immiscible or sparingly miscible with water and boil at above 100°C under normal pressure or under pressures of up to 10 atmospheres, the preferred boiling points being from 60 to 190°C under normal pressure. Suitable solvents are aromatic hydrocarbons, e.g. benzene, toluene, ethylbenzene, *o-*, *m-* and *p*-xylene and isopropylbenzene; halohydrocarbons, especially chlorohydrocarbons, e.g. tetrachloroethylene, 1,2-dichloropropane, tetrachloroethane, carbon tetrachloride, chloroform, trichloroethane, trichloroethylene, pentachloroethane, cisdichloroethylene, 1,2-dichloroethane, methylene chloride, 1,1-dichloroethane, 1,2-dichloroethane, 1,2-cis-dichloroethylene, n-butyl chloride and 2-, 3- and iso-butyl chloride, and appropriate mixtures. The solvent is suitably used in amounts of from 5 to 1,000% by weight, preferably from 5 to 50% by weight, based on the 2-nitrooxirane starting material. Ammonia may be used in the form of an aqueous solution, in general of from 25 to 35 percent strength by weight, or as a

solution in an organic solvent, e.g. one of those mentioned above, or, advantageously, in the liquid form.

The reaction may be carried out as follows. A mixture of the starting materials and, where appropriate, of the solvent is kept at the reaction temperature for from 5 to 10 hours. The end product is then isolated from the mixture by conventional methods, e.g. by evaporation of the residual ammonia, extraction with a suitable solvent, e.g. diethyl ether, and distillation of the extract, or filtration.

The end products I which may be manufactured by the above process are valuable starting materials for the manufacture of dyes, fungicides and pharmaceuticals. The pyrazines with aliphatic substituents are flavoring agents, or additives to improve the smell and taste of foodstuffs, beverages and tobacco. On oxidation with oxidizing agents such as potassium permanganate they give pyrazine carboxylic acids which in turn give, e.g. by reaction with ammonia, cyanopyrazines which are curing agents for epoxy resins and starting materials for the manufacture of diuretics. Dicyanopyrazines and tricyanopyrazines are used as phosphors. Certain pyrazinecarboxylic acid amides are hypotensives and agents for assisting the sugar metabolism. With regard to uses, reference may be made to German Published Applications 2,140,649 and 2,216,925, published Japanese Patent Application 40,065/72 and Netherlands Patent 7,203,057.

In the Examples which follow, parts are by weight and bear the same relation to parts by volume as that of the kilogram to the liter.

EXAMPLE 1

(a) 2-Nitro-2,3-hexamethyleno-oxirane

In a stirred vessel, 31 parts by volume of 2 N sodium hydroxide solution are added to a mixture of 200 parts by volume of methanol, 41 parts by volume of 15 percent strength by weight aqueous hydrogen peroxide and 18.5 parts of 1-nitro-cyclo-ocotene-(1) ($N_D^{20}=1.5100$) at from 0 to 4°C, whilst cooling. 300 parts by volume of ice water are added to the mixture at 20°C. The reaction mixture is then stirred further for 30 minutes at room temperature after which the precipitate is filtered off. After drying, 16.3 parts of 2-nitro-2,3-hexamethyleno-oxirane (80% of theory), melting at from 35 to 36°C after recrystallization from methanol are obtained. Boiling point at 0.1 mm Hg=64°C.

(b) 2,3,5,6-Bis-hexamethylenopyrazine

14.5 parts of 2-nitro-2,3-hexamethyleno-oxirane and 100 parts by volume of liquid ammonia are shaken for 6 hours in an autoclave, at 50°C and 25 atmospheres. The solid residue left after evaporation of the ammonia in the autoclave is mixed with 100 parts by volume of water. The aqueous suspension is extracted with three times 50 parts by volume of diethyl ether, the combined ether extracts are dried and the ether is evaporated off. 9.8 parts of 2,3,5,6-bis-hexamethylenopyrazine (94% of theory) melting at from 115 to 116°C after recrystallization from acetone are obtained.

EXAMPLE 2

2,3,5,6-Tetraphenylpyrazine

12 parts of 2-nitro-2,3-diphenyl-oxirane melting at from 109 to 110°C and 100 parts by volume of liquid ammonia are shaken for 6 hours in an autoclave at 100°C and 65 atmospheres. After evaporation of the ammonia, the solid residue is treated with water and the constituent left undissolved is filtered off and recrystallized from glacial acetic acid. 5.2 parts of 2,3,5,6-tetraphenylpyrazine (54% of theory) melting at from 253 to 254°C are obtained.

EXAMPLE 3

2,5-Diethyl-3,6-diphenylpyrazine

10 parts of 3-nitro-3-ethyl-2-phenyl-oxirane (boiling point at 2 mm Hg=from 100 to 103°C) and 100 parts by volume of liquid ammonia are shaken for 6 hours in an autoclave at 50°C and 22 atmospheres; the mixture is then worked up analogously to Example 1b). 5.4 parts of 2,5-diethyl-3,6-diphenylpyrazine (72% of theory) melting at from 145 to 146°C after recrystallization from methanol are obtained.

EXAMPLE 4

2,5-Dimethyl-3,6-diphenylpyrazine

9 parts of 3-nitro-3-methyl-2-phenyl-oxirane (boiling point at 0.5 mm Hg=from 95 to 97°C) and 90 parts by volume of liquid ammonia are shaken for 6 hours in an autoclave at 60°C and 28 atmospheres. The mixture is then worked up analogously to Example 1b). 2.9 parts of 2,5-dimethyl-3,6-diphenylpyrazine (44% of theory) melting at from 126 to 127°C after recrystallization from ethanol are obtained.

WHAT WE CLAIM IS:—

1. A process for the manufacture of a pyrazine wherein a 2-nitro-oxirane bearing a free hydrogen atom in the 3-position is reacted with ammonia.

2. A process as claimed in claim 1, wherein the reaction is carried out with from 5 to 50 moles of ammonia per mole of the nitro-oxirane.

3. A process as claimed in claim 1 or 2, wherein the reaction is carried out at from 20 to 200°C.

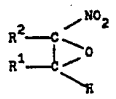
4. A process as claimed in claim 1 or 2, wherein the reaction is carried out at from 40 to 100°C.

5. A process as claimed in any of claims 1 to 4, wherein the reaction is carried out under a pressure of from 10 to 100 atmospheres.

6. A process as claimed in any of claims 1 to 5, wherein the reaction is carried out with from 5 to 1,000% by weight, based on the nitrooxirane, of a solvent which is inert under the reaction conditions.

7. A process as claimed in any of claims 1 to 6, wherein the reaction is carried out with a solvent which is inert under the reaction conditions and boils at above 100°C under normal pressure or under pressures of up to 10 atmospheres.

8. A process as claimed in any of claims 1 to 7, wherein the 2-nitrooxirane starting material has the formula



in which R^1 and R^2 are identical or different and are each hydrogen, alkyl of 1 to 10 carbon atoms, cyclopentyl, cyclohexyl, aralkyl of 7 to 12 carbon atoms, phenyl or naphthyl or form together with the carbon atoms to which they are attached an alicyclic ring of 5 to 12 ring members, the radicals and rings being optionally substituted by one or more substituents which are inert under the reaction conditions.

9. A process as claimed in claim 8 wherein a 2-nitrooxirane specifically named herein is employed.

10. A process for the manufacture of a pyrazine carried out substantially as described in any of the foregoing Examples.

11. Pyrazines when manufactured by a process as claimed in any of claims 1 to 10.

12. Pyrazine carboxylic acids when obtained by oxidation of pyrazines claimed in claim 11 with an oxidizing agent.

13. Cyanopyrazines when obtained by reaction of pyrazine carboxylic acids claimed in claim 12 with ammonia.

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